A prospective study comparing clonidine and diazepam for maternity remaining education, anxiolysis, and postoperatal pain management in pediatric patients

Venkata radhakrishna varadapureddi[1], dr n.s. lakshmi pallavi[2]

[1]associate professor, melmaruvathur adhiparasakthi institute of medical sciences and research, melmaruvathur, chengalpattu district, tamilnadu, india 603319.

[2] assisstant professor, department of anaesthesiology, arunai medical college and hospital, velu nagar, mathur, tiruvannamalai

Abstract

This prospective study aimed to compare the efficacy of clonidine (2 mg/kg and 4 mg/kg), as a premedication in children undergoing reconstructive, orthopaedic, otological, or ophthalmological surgery to that of diazepam (0.2 mg/kg). One hundred children asa grade i, aged 3-15 years were taken and randomly assorted into three groups, clonidine 2 mg/kg (2c), clonidine 4 mg/kg (4c), and diazepam 0.2 mg/kg (d). Each group received the respective premedication 90 minutes prior to induction of anaesthesia. The research variables were sedation, parental separation, mask acceptance and pain scores perioperative period. The groups that received clonidine expressed a significantly higher sedation, parental separation, and mask acceptance compared to diazepam group. The clonidine groups had also lower pain scores, and required less rescue analgesia. Also, clonidine provided no pertinent changes in the respiratory frequency or desaturation, not to mention that no severe respiratory depression was observed. However, clonidine 4 mg/kg resulted in minor incidence of hypotension and bradycardia that required conservative postoperative monitoring. The outcomes revealed that clonidine particularly at 2mg/kg dose is a nice and safer alternative of diazepam in premedication of children, which offers sedative, anxiolytic and analgesic effects with minimal side effects.

Keywords: clonidine, pediatric premedication, sedation, analgesia, anaesthesia

Introduction

Anxiety and discomfort are two factors that contribute to the realization of high levels of emotional strain among the children. Alpha-2 agonists new findings in the area of alpha-2 agonists suggest the potential sedative and analgesic (pain-reliever) effect of clonidine [1-5]. In addition, its bioavailability via the mouth is good. The possibility to achieve sedation, analgesia and the single dose of a single drug by oral route and other favorable effects induced us to investigate its usability as a premedication in children [6-8]. Due to the potential side effects, which are low blood pressure and slow heart rate, we investigated the effect of the drug administered at two doses (2 or 4 mg/kg) in order to determine the optimal dose [9-13].

Materials and methodology

Big a 100 children aged 3-15 years who were asa grade i and underwent either reconstructive, orthopaedic, otological or ophthalmological operations were included as prospective study. The patients were randomly divided based on computer-generated random table into three groups, 2c, 4c, and d groups. The children of these groups were premedicanted; with clonidine 2 or 4 mg/kg

or diazepam 0.2 mg/kg respectively and atropine 0.03 mg/kg orally 90 minutes before induction of anaesthesia [1-5].

Premedication consisted of clonidine and diazepam, crushed tablet of clonidine 100 mg (arkamine) and diazepam 5 mg (calmpose) were dissolved in 10 ml of 5 per cent dextrose. The remaining management (that also included the observations) was done by the second anaesthesiologist who was not informed about the premedication given. The variables measured were heart rate (hr), systolic bp (sbp), diastolic bp (dbp), and respiratory rate (rr) before and at 30-minute intervals follow ing premedication. The level of sedation was also charted on a three-point scale [1= tearful/combative, 2= alert/aware, 3= drowsy/sleepy] [6-15]. The scores of parental separations (how the child acted when he/she entered the theatre) were determined in three points [1= poor (anxious and combative), 2= good (anxious but easily reassured), 3= excellent (sleepy and calm)]. The concentration of n 2 o that the children were exposed to was 50 percent and 0.5 to 3 percent of halothane in oxygen using a mask. A quality of mask acceptance was defined as a four-point scale [1= poor (combative and angry), 2= fair (fearful and not easily calmed), 3= good (fearful but easily calmed), 4= excellent (unafraid and cooperative)]. Iv line was achieved in case the child was co-operative. Otherwise, inhalational induction was maintained until the child allowed the iv access to be inserted. Thiopentone was then followed by vecuronium and three minutes later tracheal intubation was performed. The anaesthetic maintenance was controlled ventilation with 66 per cent n2o and 0.5 to 3 per cent halothane in oxygen. No additional sedative and analgesic were used [16-21]. The recovery room observed all the children during six hours following the operation. Objective pain scale (ops, 0-10), alderate recovery score and postoperative sedation levels were determined at 30 minutes interval during the first two hours and at one hour interval during the next six hours. The sedation depth in the postoperative region was also measured using a four-point scale [0= awake and crying; 1= awake and settled; 2= drowsy but can be roused with a mild stimulation, 3= unrousable]. The frequencies of the adverse effect were noticed in hypotension (sbp < 70 mmhg), hypertension (sbp > 140 mmhg), bradycardia (hr < 60/min), respiratory depression (rr < 12/min), desaturation (spo2 < 90% during 15 seconds), postoperative nausea and vomiting (ponv), and shivering. Atropine was used to treat bradycardia. Hypotension was to be corrected using iv fluids, when it was accompanied by bradycardia atropine was administered and in case it was persistent and severe dopamine infusion was to be started. Rescue analgesic which consisted of pentazocine 0.3mg/kg and promethazine 0.2mg/kg was administered in the instance that the ops was greater than six in the recovery room. Nonetheless, we gave an opportunity of 15-30 minutes of observation time to define whether the patient will react to parental reassurance and consolation. Then at 6 hours, the children were transferred to the ward. Syrup ibugesic (ibuprofen and paracetamol) was used in the ward when ops was greater than six. The highest ops was recorded during the first six hours of every patient. It was on this that it was employed to determine the average maximal ops per group and also, what percentages of patients have encountered different levels of pain; pain-free (ops 0-3), mild pain (ops 4-6) and severe pain (ops 7-10).

Results

Table - 1: demographic characteristics

Parameters	Clonidine 2 mg/kg	Clonidine 4 mg/kg	Diazepam 0.2 mg/kg
Number	33	33	34
Age (years)	6.85±3.12	7.10±2.88	6.90±2.45
Sex (m : f)	25 : 8	22 : 11	18 : 16
Weight (kg)	20.58±5.92	18.47±6.30	19.15±5.16
Duration of surgery (min)	85.55±33.62	89.22±37.80	78.80±28.47
Duration of anaesthesia (min)	93.12±35.48	90.44±38.27	80.72±29.09
Premedication time (min)	92.17±6.14	95.45±7.01	97.14±6.12

Table - 2: main features

Parameters	Clonidine 2 mg/kg	Clonidine 4 mg/kg	Diazepam 0.2 mg/kg
N	33	33	34
Parental separation score	2.24±0.63	2.29±0.61	1.72±0.55 ***
Mask acceptance score	3.12±0.91	3.14±0.98	1.58±0.72 ***
Highest ops in 1st 6 hrs	5.12±1.44	5.02±1.69	7.89±1.18 **
Rescue analgesia (0 - 6 hours)	6 (18%)	7 (21%)	30 (88%) ***
Rescue analgesia (6 - 24 hours)	1 (3%)	2 (6%)	15 (44%) ***

This prospective study was undertaken to assess efficacy of clonidine (2 mg/kg and 4 mg/kg), and diazepam (0.2 mg/kg) as premedicants in pediatric patients, who were poly-surgery. The demographic characteristics of the participants of the research were similarly distributed in the three groups since there were 33 children in clonidine 2 mg/kg group, 33 children in clonidine 4 mg/kg group and 34 children in diazepam 0.2 mg/kg group. The mean age of clonidine 2 mg/kg group was 6.85 years (3.12), clonidine 4 mg/kg group was 7.10 years (2.88) and 6.90 years (2.45) in diazepam 0.2 mg/kg group. The majority of them were males and the male to female ratio in clonidine 2mg/ kg group was 25:8, in clonidine 4 mg/ kg group was 22:11 and diazepam 0.2 mg/ kg group was 18:16. The average weight of the children was 20.58 kg (5.92), 18.47 kg (6.30) and 19.15 kg (5.16) in clonidine 2 mg/ kg, clonidine 4 mg/ kg and diazepam groups

respectively. The surgery mean time was 85.55 minutes (33.62), 89.22 minutes (37.80) in clonidine 2 mg/kg and 78.80 minutes (28.47) in diazepam group. Clonidine 2 mg/kg, clonidine 4 mg/kg and diazepam required 92.17 (6.14), 95.45 (7.01) and 97.14 (6.12) minutes concerning the main features, the scores of parental separation and mask acceptance were higher in both clonidine 2mg/kg and 4mg/kg than the diazepam group with scores of 2.24+/-0.63 and 2.29+/-0.61 and 1.72+/-0.55, respectively. The peak objective pain score (ops) in the initial six hours was also much lower in diazepam group (7.89±1.18), when compared to 5.12+/-1.44 in clonidine 2 mg/kg and 5.02+/-1.69 in clonidine 4 mg/kg. Eighty eight percent of children in the diazepam group needed rescue analgesia within the first 6 hours as opposed to 18 percent and 21 percent in clonidine 2 mg/kg and 4 mg/kg groups respectively. The analgesia rescue between 6 to 24 hours was also required more in diazepam group where 44 percent of the children took extra medicine as compared to 3 percent and 6 percent in clonidine 2 mg/kg and 4 mg/kggroup. These findings suggested that, clonidine (especially the 2mg/kg and 4 mg/kg doses) provided better premedication quality and needed less rescue analgesia as compared to diazepam.

Figure1:demographic characteristics comparison all parameters across three treatment groups (n=33, 33, 34)

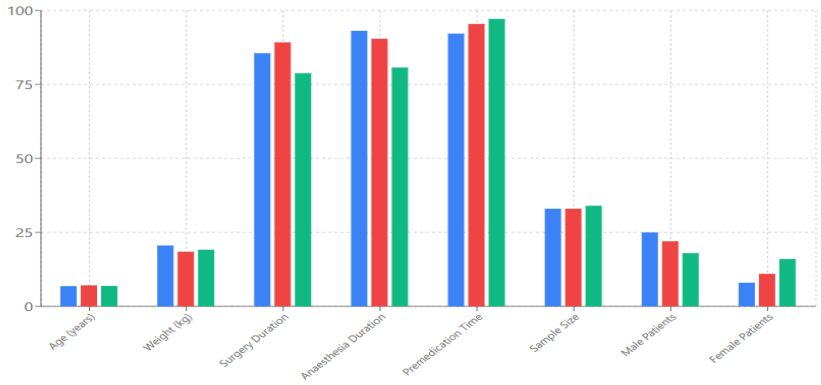
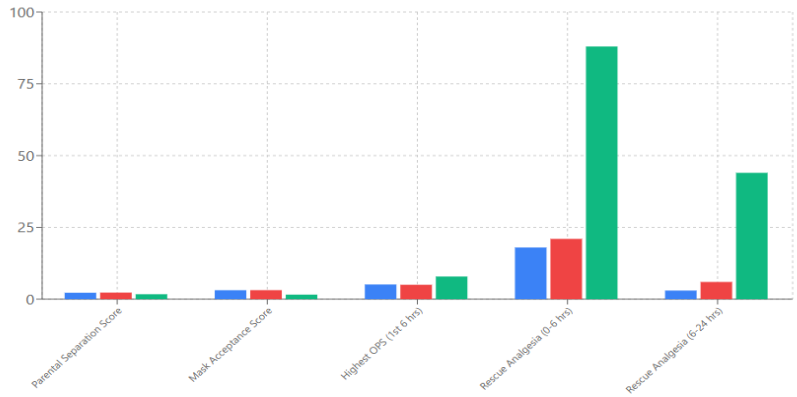


Figure2: main clinical features comparison all clinical outcomes across three treatment groups (n=33, 33, 34)



Discussion

In the last several years, several studies provided an idea about the usefulness of the alpha-2 agonist during the perioperative period. Oral clonidine 0.3 mg has been identified to cause sedation and anxiolysis in adult patients. Carabine et al. Observed that the sedative effect was dose-dependent with 0.2 mg dose having anxiolytic effect. Neuraxial administration of clonidine early in animals and subsequently in man has been profound in regard to analgesia. Oral clonidine is not a common preference in pain management as it is not as effective as the neuraxial route, but two things make it special: a) it has an indication in upper dermatological surgeries, and b) it is the most easy and acceptable route in children [1-5]. Mikawa et al. Showed lower pain scores, longer pain-free interval, and less rescue analgesics in the children premeditated with 4c compared to 2c and control group. Our study was an evaluation of the efficacy of clonidine as a premedication in a single oral dose in sedation, anxiolysis and postoperative pain reduction. Opioids were not involved in the study, as their application was associated with respiratory depression, nausea, vomiting, pruritus, as well as the need to apply painful injections. Children under the age of two years were not involved in the study since the cardiac output of the younger children is heart rate dependent and clonidine has been found to cause bradycardia. We have discovered that the clonidine treated groups yielded a much better sedation compared to the diazepam group with the sedation effect reaching its peak at 90 minutes; the same time that the peak concentration of clonidine plasma occurs after an oral administration [6-15]. Once more in agreement with mikawa et al., the parental separation and acceptance of the mask were superior in both clonidine groups and a greater number of patients treated with clonidine accepted intravenous (iv) induction in our study too. This shows that clonidine premedication comes in handy in relaxing and sedating the children and thus, iv access can be easily established. Similar to other reports, respiratory frequency did not vary significantly with clonidine premedication and there was no instance of respiratory depression or desaturation post operatively. Reduction of heart rate was however significantly noted in clonidine treated groups and systolic blood pressure was significantly reduced only in 4c group. Haemodynamic response to intubation blunting is usually not so significant in kids but it may be beneficial in kids with a threat of cerebrovascular accidents or those with renal hypertension or cardiac insufficiency. They found no serious postoperative complications in the form of hypotension or bradycardia, which is likely due to atropine premedication. We have also shown that clonidine reduces anaesthetic requirements which was not precisely measured in our study due to sporadic administration of halothane. Regarding the pain scores, the patients treated with clonidine recorded lower pain scores in the first 90 minutes and six hours, compared to diazepam group. Rescue analgesia was required in 96 percent of diazepam group patients at 90 minutes and pain scores were comparable up to the fifth hour. An increased score of pain was observed in diazepam group at sixth hour probably due to wearing off effect of pentazocine. Only 16 per cent of the children treated with clonidine experienced severe pain and 16-20 per cent of the children did not experience any pain even though no analgesic had been administered before. In addition to that, children who received clonidine were calm and silent compared to diazepam group where majority of them were crying and alert. The 4c group had only one child who could not be aroused and others were not oversedated. Jorris et al, has demonstrated usefulness of iv clonidine in preventing postoperative shivering and in our study also we observed less number of shivering incidences in clonidine treated patients. Oral clonidine peak plasma concentration of 90 minutes and its long half-life helped in the attenuation of shivering in minor surgeries. As much as the effects are desirable, hypotension and bradycardia that are the greatest side effects of clonidine

happened in 8 percent of the 4c group patients and 4 percent of 2c group patients thus close postoperative observation is required. On the other hand, the research patients who received diazepam recorded cases of hypertension, but this went away once the pain started emerging [16-21]. In conclusion, 2c and 4c clonidine premedication offered quiet, cooperative children, who had great sedation, anxiolysis, analgesia and facilitated separation with parents. Despite the fact that clonidine 4c was connected with the higher incidence of hypotension, clonidine 2c showed the same outcome with the fewer number of complications and, thus, is the more sensible option as far as the small surgeries are concerned, though the postoperative monitoring is still greatly recommended.

Conclusion

This research proves that clonidine is an effective premedication in children and its use shows considerable advantages in sedation, anxiolysis and postoperative analgesia. The dose of clonidine 2 mg/kg, as well as 4 mg/kg, was better than diazepam in producing optimal sedation and anxiety score, and children treated with clonidine showed better parental separation and mask acceptance. In addition, it was observed that clonidine made intravenous access much easier because of its sedative properties which is very important in anaesthesia in children. Although clonidine premedication did not show any significant changes in the respiratory frequency and postoperative desaturation, it caused a small decrease in the heart rate, especially in the 4c group. Notably, no case of severe respiratory depression, typical of other sedatives and opioids, occurred. Clonidine too had great analgesic effect, whereby the amount of rescue analgesia needed by the clonidine-treated patients was less than that of diazepam group. The pain scores at the 90 minutes and six hours interval were also significantly lower in the clonidine groups, which demonstrated its analgesic effect despite lacking opioids. Although the benefits, clonidine particularly the 4c group was also linked with a minor occurrence of hypotension and bradycardia, which addressed the need to monitor the patients closely in the postoperative period. Nevertheless, clonidine at 2 mg/kg was found to be a perfect match in minor surgical procedures since it provided excellent sedation and analgesia with insignificant adverse effects. Clonidine 2c could be the ideal choice to use in pediatric premedication in outpatient procedures due to its long half-life and safety profile, which would result in a calm, cooperative, and pain-free procedure in children.

References

1. Maze m, tranquilli w. Alpha-2 adrenoceptor agonists. Defining the role in clinical anaesthesia. Anesthesiology 1989; 74: 581-605.
2. Hayashi y, maze m. Alpha2 adrenoceptor agonists and anaesthesia. Br j anaesth 1993; 71: 108-18.
3. Tong c, eisenach jc. Alpha-2 adrenergic agonists. Anesthesiology cinics of north america 1994; 12: 49-63.
4. Khan jp, ferguson cn, jones rm. Alpha-2 and imidazolin receptor agonists. Anaesthesia 1999; 54: 146-65.
5. Wright pmc, carabine ua, mc clune s, orr da, moore j. Preanaesthetic medication with clonidine. Br j anaesth 1990; 65: 628-32.
6. Carabine ua, wright pmc. Moore j. Preanaesthetic medication with clonidine: a dose response study. Br j anaesth1991; 67: 79-83.

7. Paalzow l. Analgesia induced by clonidine in mice and rats. Journal of pharmacy and pharmacology. 1974; 26: 361-63.
8. Bonnet f, boico o, rostaing s et al. Extradural clonidine analgesia in postoperative patients. Br j anaesth 1989; 63(3):465-69.
9. Filos ks, goudas lc, patroni o, polyzou v. Intrathecal clonidine as a sole analgesic for pain relief after caesarean section. Anesthesiology 1992; 77: 267-74.
10. Jamali s, monan s, begon c et al. Clonidine in paediatric caudal anaesthesia. Anesth analg 1994; 78: 663-66.
11. Segal is, jarvis dj, duncan sr, white pe. Maze m. Clinical efficacy of oral and transdermal clonidine combination during the perioperative period. Anesthesiology 1991; 74: 220-25.
12. Mikawa k, nishina k, maekawa n, obara h. Oral clonidine premedication reduces postoperative pain in children. Anesth analg 1996; 82: 225-30.
13. Mikawa k, maekawa n, nishina k, takao y, yaku h. Obara h. Efficacy of oral clonidine premedication in children. Anesthesiology 1993; 79: 926-31.
14. Jarvis da, duncan sr, segal is, maze m. Ventilatory effects of clonidine alone and in the presence of alfentanil, in human volunteers. Anesthesiology 1992; 76: 899-905.
15. Ghignone m, quintin l, duke pc, kehler ch. Calvillo o. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anaesthesia and endotracheal intubation. Anesthesiology 1986; 64: 36-42.
16. Ghignone m, calvillo o, quintin l. Anaesthesia and hypertension: the effect of clonidine on preoperative hemodynamics and isoflurane requirements. Anesthesiology 1987; 67: 3-10.
17. Pouttu j, scheinin b, rosenberg ph, viinamaki o. Scheinin m. Oral premedication with clonidine: effects on stress responses during general anaesthesia. Acta anaesthesiologica scandinavica 1987; 31: 730-34.
18. Flack jw, bloor bc, flack we, wong d, dazza s, stead sw, laks h. Reduced narcotic requirements by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987; 67: 11-19.
19. Joris j, banache m, bonnet f. Clonidine and ketancerin both are effective treatment for postanesthetic shiveringanesthesiology 1993; 79: 532-39.
20. Orko r, pouttu j, ghignone m, rosenberg ph. Efficacy of clonidine on haemodynamic responses to endotracheal
21. Intubation and on gastric acidity. Acta anaesthesiologica scandinavica 1987; 31: 325-29.